A transnational collaborative network dedicated to the study and applications of the vascular endothelial growth factor-A in medical practice

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Letter to the Editor

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A transnational collaborative network dedicated to the study and applications of the vascular endothelial growth factor-A in medical practice: the VEGF Consortium

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To the Editor,

The Vascular Endothelial Growth Factor European Genomic Federation (VEGF) Consortium (www.vegfconsortium.org) was founded in June 2014 by Sophie Visvikis-Siest (chair of the consortium) and an international group of researchers with an interest focused on VEGF-A and its implications in personalized medicine.

Here, we present the VEGF Consortium and describe its objectives and ambitions, its structure and its components together with the methodologies used in projects and preliminary results.

The VEGF Consortium aims to develop a transnational collaborative network dedicated to large integrative and multidisciplinary genomic studies of the VEGF-A in order to generate applicable knowledge for medical practice thanks to the following specific objectives:

- to combine data from multiple cohorts in order to identify VEGF-A '-omics' profiling in health and non-communicable diseases
- to elucidate the pivotal role of VEGF-A in the pathophysiology of non-communicable diseases
- to demonstrate the patients' stratification potential of VEGF-A '-omics' profiling
- to implement the research results into clinical practice and establish the role of VEGF-A as a predictive, preventive, diagnostic and prognostic biomarker
- to provide information on the effect of VEGF-A '-omics' profiling in side effects and response to therapy through pharmacogenomics studies

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- to propose implementation strategies and European guidelines involving VEGF-A '-omics' profiling for the management of non-communicable diseases
- to share methodologies, data and knowledge in the field of '-omics' management and innovative statistics
- to develop standardized teaching and evaluation methods practiced and validated by the consortium.

It comprises 11 working groups, where the partners of the consortium are participating based on their expertise:

1. VEGF-A '-omics' profiling in health
2. VEGF-A '-omics' profiling in diseases
3. '-Omics' technologies
4. Methodological aspects
5. VEGF-A clinical implementation
6. Pharmagenomics
7. Endothelins and endothelial factors
8. VEGF-A basic research (cancer cell lines, animal models)
9. VEGF-A and inflammation
10. Communication and scientific/educational meetings
11. Raising awareness of populations

Prospective, longitudinal, family-based or population-based cohorts of healthy individuals are the core of the consortium. These are the following:

1. The STANISLAS family study: This is a longitudinal family structure cohort of community-based population of French origin recruited in 1993–1995, followed up for 15 years. A number of 1006 nuclear families comprising two parents and at least two biological children over 6 years old are included in the study [1].
2. The Framingham Heart Study: It is an ongoing, longitudinal, community-based, observational cohort study that was initiated in 1948 to prospectively investigate the risk factors for cardiovascular disease (CVD). The original cohort enrolled 5209 men and women, the offspring cohort enrolled 5124 participants (including 3514 biological offspring) and Gen 3 included 4095 individuals [2–4].
3. Cilento study: This is a population-based study that aims at identifying genetic risk factors for common diseases and traits. The sample includes isolated populations from three villages (Campora, Gioi and Cardile). The overall sample size of individuals participating to the study is 2100 [5].
4. The LifeLines Cohort Study and Biobank (LLs): LLs is a multidisciplinary prospective population-based cohort study examining the health and health-related behaviors of 167,000 persons living in the north east region of The Netherlands in a three-generation design [6].

Furthermore, cohorts of patients and case-control studies are also included in the consortium:

5. The Hellenic Study of Interactions between SNPs and Eating in Atherosclerosis Susceptibility: case-control study of coronary artery disease.
6. Ljubljana patients: case-control studies recruited from Ljubljana, Slovenia that include cases of osteoporosis, osteoarthritis, CVD and diabetes [7–9].

In addition, partners of the consortium have access to large biobanks such as the UK Biobank (Panagiotis Deloukas), Biobanking and Biomolecular Resources Research Infrastructure – European Research Infrastructure Consortium BBMRI-ERIC (including Sophie Visvikis-Siest with the Biological Resources Center IGE-PCV – BB-0033-00051) and the Alliance for Clinical Trials in Oncology (Federico Innocenti).

Given the wide range of the research field and the need for application of different methodologies in order to successfully achieve its objectives, the consortium is composed of scientists with different and complementary expertise and with a large range of resources such as large study populations, research materials and harmonized data.

Although the VEGF Consortium was officially founded on 2014, it was based on the long-term collaboration between some of its founding partners. Therefore, a number of significant results have been published already, and many projects are ongoing, with promising preliminary results.

Among the most basic steps was the identification through two genome-wide association studies (GWAS) of 10 genetic variants that explain >50% of the circulating VEGF-A levels variability [10, 11]. This is a unique finding among GWAS. In most GWAS, the identified variants do not explain >10% of the individual variability of the assessed traits. This finding has strengthened our belief that VEGF-A will indeed be used as strong biomarker for personalized medicine. Significant associations between some of these polymorphisms and intermediate phenotypes of chronic diseases have been identified since then: high-density and low-density lipoprotein [12], L-selectin gene expression [13] and free tri-iodothyronin (FT3) levels [14]. Significant epistatic interactions between these variants were observed for intercellular adhesion molecule 1 (ICAM-1), E-selectin, interleukin 6 and tumor necrosis factor α (TNF-α) plasma levels [13]. Concerning specific disease risk, we have shown

that these polymorphisms and/or their epistatic interactions can affect the risk for depression [15], and for autoimmune thyroid diseases [14], whereas no associations were found for diabetes type 2 [16].

Concerning the expression isoforms of *VEGF-A* gene, we have shown that these are significantly associated with ICAM-1, L-selectin and TNF-α expression [13] and with specific autoimmune thyroid diseases [17].

Furthermore, we have also identified associations between VEGF-A circulating levels and thyroid hormones levels [17] and with ICAM-1 and E-selectin levels [13].

Through a candidate gene approach of polymorphisms in genes involved in angiogenesis, we have identified direct and epistatic effects of variants on nitric oxide synthase 3 (*NOS3*), *CD14*$^{+}$ monocytes, matrix metalloproteinases (*MMPs*) and interleukin 4 receptor (*ILR4*) genes with levels of VEGF-A and VEGF-A expression isoforms, but also gene × environment interactions [18].

An important result is also the production of two patents based on the results of studies performed by partners of the consortium [19, 20].

Several projects are ongoing and focused on CVD intermediate phenotypes, thyroid diseases, cancer and stroke.

Three face-to-face meetings have been organized to date: Paris (2014), Budapest (2015) and Santorini (2016).

The VEGF Consortium is an ambitious international collaboration that aims to pave the way for the implementation of VEGF-A in personalized medicine and routine clinical practice. The designed projects take advantage of the wide expertise of its partners, the large infrastructures of cohorts and biobanks and a combination of the most up-to-date "-omics" approaches for generating multidimensional data, as well as 'systems medicine' approaches, network analysis and computational modeling methodologies.

Among its major originalities is that it integrates commercialization and communication platforms, targeting the valid and easy measurement of the identified biomarkers in large-scale settings but also the education of the general population, patients, scientists and health practitioners.

The VEGF Consortium is a novel consortium with an innovating structure and original goals. The ultimate goal is to ameliorate life expectancy, quality of life for individuals and financial benefits for health systems.

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